

What is claimed:

1. A method of detecting whether a subject is either predisposed to or afflicted with a pulmonary disease which comprises (1) obtaining a suitable sample from the subject; and (2) detecting in the sample a bone morphogenetic protein receptor-II mutation which is not present in wildtype bone morphogenetic protein receptor-II,
wherein the presence of a mutation indicates that the subject is predisposed to or afflicted with the pulmonary disease.
2. The method of claim 1, wherein the suitable sample is a nucleic acid sample, and the mutation is detected in a nucleic acid encoding bone morphogenetic protein receptor-II.
3. The method of claim 1, wherein the suitable sample is one which comprises a bone morphogenetic protein receptor-II polypeptide, and the mutation is detected in the bone morphogenetic protein receptor-II polypeptide.
4. The method of claim 1, wherein the pulmonary disease is Primary Pulmonary Hypertension.
5. The method of claim 4, wherein the Primary Pulmonary Hypertension is Familial Primary Pulmonary

Hypertension.

- 5 6. The method of claim 1, wherein a bone morphogenetic protein receptor-II polypeptide is encoded by a gene which is located on chromosome 2q34.
- 10 7. The method of claim 1, wherein a wildtype nucleic acid encoding a bone morphogenetic protein receptor-II polypeptide comprises consecutive nucleotides comprising the nucleic acid sequence set forth in SEQ ID NO: 1.
- 15 8. The method of claim 1, wherein a wildtype bone morphogenetic protein receptor-II polypeptide comprises consecutive amino acids comprising the amino acid sequence set forth in SEQ ID NO: 2.
- 20 9. The method of claim 1, wherein the mutation results in a truncated bone morphogenetic protein receptor-II.
- 25 10. The method of claim 2, wherein the mutated nucleic acid comprises a deletion of a nucleotide segment guanosine-guanosine-guanosine-adenosine located at positions 1099-1103 in a wildtype nucleic acid, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
11. The method of claim 3, wherein the mutated bone

morphogenetic protein receptor-II polypeptide comprises a frameshift mutation at a glutamic acid residue located at position 368 in the wildtype polypeptide, which wildtype polypeptide comprises the amino acid sequence set forth in SEQ ID NO:2.

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12. The method of claim 2, wherein the mutated nucleic acid comprises a deletion of a thymidine residue located at position 2579 in a wildtype nucleic acid, which wildtype nucleic acid comprises the sequence set forth in Seq ID NO:1.

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13. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a frameshift mutation at an asparagine residue located at position 861 in the wildtype polypeptide, which wildtype polypeptide comprises the amino acid sequence set forth in SEQ ID NO:2.

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14. The method of claim 2, wherein the mutated nucleic acid comprises a replacement of a nucleotide segment cytosine-thymidine-thymidine-thymidine located at positions 507-510 in a wildtype nucleic acid with a nucleotide segment adenosine-adenosine-adenosine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.

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15. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a mutation of a cysteine located at position 169 in a wildtype polypeptide to a termination codon, which

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wildtype polypeptide comprises the sequence set forth in SEQ ID NO:2.

16. The method of claim 2, wherein the mutated nucleic acid comprises a mutation of a cytosine located at position number 2617 in a wildtype nucleic acid to a thymidine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.

17. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a mutation of an arginine located at position 873 in a wildtype polypeptide to a termination codon, which wildtype polypeptide comprises the sequence set forth in SEQ ID NO:2.

18. The method of claim 2, wherein the mutated nucleic acid comprises a replacement of a nucleotide segment adenosine-guanosine present at positions 690-691 in a wildtype nucleic acid with a thymidine residue, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.

19. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a frameshift mutation at a lysine residue located at position 230 in a wildtype polypeptide, which wildtype polypeptide comprises the sequence set forth in SEQ ID NO:2.

20. The method of claim 2, wherein the mutation is a missense mutation.
- 5 21. The method of claim 2, wherein the mutated nucleic acid comprises a mutation of a cytosine located at position number 1471 in a wildtype nucleic acid to a thymidine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
- 10 22. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a mutation of an arginine located at position 491 in a wildtype polypeptide to a tryptophan, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.
- 15 23. The method of claim 2, wherein the mutated nucleic acid comprises a mutation of a guanosine located at position number 1472 in a wildtype nucleic acid to an adenosine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
- 20 24. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a mutation of an arginine located at position number 491 in a wildtype polypeptide to a glutamine, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.
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- 5 25. The method of claim 2, wherein the mutated nucleic acid comprises a deletion of a nucleotide segment adenosine-thymidine-thymidine-thymidine located at positions 1248-1251 in a wildtype nucleic acid, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
- 10 26. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a mutation of an phenylalanine located at position number 417 in a wildtype polypeptide to a stop codon, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.
- 15 27. The method of claim 2, wherein the mutated nucleic acid comprises a mutation of a cytosine located at position number 994 in a wildtype nucleic acid to a thymidine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
- 20 28. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a mutation of an arginine located at position number 332 in a wildtype polypeptide to a stop codon, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.

29. The method of claim 2, wherein the mutated nucleic acid comprises a mutation of a thymidine located at position number 295 in a wildtype nucleic acid to a cytosine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.

30. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a mutation of a cysteine located at position number 99 in a wildtype polypeptide to an arginine, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.

31. The method of claim 2, wherein the mutated nucleic acid comprises a deletion of a guanosine residue located at position 1097 in a wildtype nucleic acid, which wildtype nucleic acid comprises the sequence set forth in Seq ID NO:1.

32. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a frameshift mutation at a proline residue located at position 366 in the wildtype polypeptide, which wildtype polypeptide comprises the amino acid sequence set forth in SEQ ID NO:2.

33. The method of claim 2, wherein the mutated nucleic acid comprises a mutation of a guanosine located at position number 727 in a wildtype nucleic acid to a thymidine,

which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.

- 5 34. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a mutation of a glutamic acid located at position number 243 in a wildtype polypeptide to a stop codon, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.

- 10 35. The method of claim 2, wherein the mutated nucleic acid comprises a deletion of an adenosine residue located at position 1214 in a wildtype nucleic acid, which wildtype nucleic acid comprises the sequence set forth in Seq ID NO:1.

- 15 36. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a frameshift mutation at an aspartic acid residue located at position 405 in the wildtype polypeptide, which wildtype polypeptide comprises the amino acid
20 sequence set forth in SEQ ID NO:2.

- 25 37. The method of claim 2, wherein the mutated nucleic acid comprises a deletion of a nucleotide segment adenosine-cytosine located at positions 2441-2442 in a wildtype nucleic acid, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.

38. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises

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39. The method of claim 2, wherein the mutated nucleic acid comprises a mutation of a cytosine located at position number 2695 in a wildtype nucleic acid to a thymidine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
40. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a mutation of an arginine located at position number 899 in a wildtype polypeptide to a stop codon, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.
41. The method of claim 2, wherein the mutated nucleic acid comprises a deletion of a nucleotide segment present at positions 189-209 in a wildtype nucleic acid, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
42. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a deletion of an amino acid segment serine-threonine-cysteine-tyrosine-glycine-leucine-tryptophan located at position numbers 64-70 in a wildtype polypeptide, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.

43. The method of claim 2, wherein the mutated nucleic acid comprises a mutation of a guanosine located at position number 296 in a wildtype nucleic acid to a adenosine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
44. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a mutation of a cysteine located at position number 99 in a wildtype polypeptide to a tyrosine, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.
45. The method of claim 2, wherein the mutated nucleic acid comprises a mutation of a thymidine located at position number 250 in a wildtype nucleic acid to a cytosine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
46. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a mutation of a cysteine located at position number 84 in a wildtype polypeptide to an arginine, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.
47. The method of claim 2, wherein the mutated nucleic acid comprises a mutation of a guanosine located at position number 1040 in a wildtype nucleic acid to a adenosine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
48. The method of claim 3, wherein the mutated bone

morphogenetic protein receptor-II polypeptide comprises a mutation of a cysteine located at position number 347 in a wildtype polypeptide to a tyrosine, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.

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49. The method of claim 5, wherein the subject is suffering from an asthmatic symptom, so as to thereby prevent a subject afflicted with Familial Primary Pulmonary Hypertension from being misdiagnosed as asthmatic.

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50. The method of claim 49, wherein the asthmatic symptom is wheezing or intermittent shortness of breath.

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51. A method of predicting an increased likelihood of a subject giving birth to twins or triplets which comprises:

a) obtaining a suitable nucleic acid sample from the subject;

b) detecting the presence of one copy of a mutant nucleic acid which encodes a bone morphogenetic protein receptor-II polypeptide, thereby indicating that the subject is heterozygous for the mutation,

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wherein heterozygosity predicts an increased likelihood of the subject giving birth to twins or triplets.

52. A method of predicting an increased likelihood of a

subject having a miscarriage prior to giving birth to a child which comprises:

a) obtaining a suitable nucleic acid sample from the subject;

5 b) detecting the presence of two copies of a mutant nucleic acid which encodes a bone morphogenetic protein receptor-II polypeptide, thereby indicating that the subject is homozygous for the mutation,

10 wherein homozygosity predicts an increased likelihood of the subject having a miscarriage prior to giving birth to a child.

53. A method of preventing and/or treating Familial Primary
15 Pulmonary Hypertension in a subject which comprises introducing a nucleic acid encoding a wildtype bone morphogenetic protein receptor-II polypeptide operably linked to a promotor into a suitable cell under conditions such that the nucleic acid expresses the
20 wildtype bone morphogenetic protein receptor-II protein so as to thereby prevent and/or treat Familial Primary Pulmonary Hypertension in the subject.

54. The method of claim 53, wherein the suitable cell is a
25 lung cell.

55. A method of preventing and/or treating Familial Primary Pulmonary Hypertension in a subject which comprises administering to the subject an effective amount of a

wildtype bone morphogenetic protein receptor-II polypeptide comprising consecutive amino acids having the sequence set forth in SEQ ID NO:2 to prevent and/or treat Familial Primary Pulmonary Hypertension in the subject.

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56. A method of detecting whether a subject is either predisposed to or afflicted with Familial Primary Pulmonary Hypertension which comprises:

- 10 a) obtaining a suitable nucleic acid sample from the subject; and
- b) detecting the presence of a (GGC)₁₂ trinucleotide repeat at positions -928 to -963 in the 5' end of the bone morphogenetic protein receptor-II gene,

15 wherein the presence of the trinucleotide repeat indicates that the subject is either predisposed to or afflicted with Familial Primary Pulmonary Hypertension.

20 57. A method of screening for a compound capable of treating Familial Primary Pulmonary Hypertension which comprises:

- a) contacting a cell which expresses a mutant bone morphogenetic protein receptor-II with the compound; and
- 25 b) determining whether the compound is capable of reversing the functional deficit present in Familial Primary Pulmonary Hypertension in the cell,

wherein a reversal of the functional deficit in the

cell indicates that the compound is capable of treating Familial Primary Pulmonary Hypertension.

5 58. The method of claim 57, wherein the functional deficit is reduced kinase activity for the bone morphogenetic protein receptor-II.

59. A method of obtaining a composition which comprises:

- 10 a) identifying a compound capable of treating Familial Primary Pulmonary Hypertension by the method of claim 57; and
- b) admixing the compound so identified or a homolog or derivative thereof with a carrier.

15 60. A transgenic non-human animal whose cells comprise a mutant nucleic acid which encodes a bone morphogenetic protein receptor-II polypeptide.

20 61. The transgenic non-human animal of claim 60, wherein the non-human animal exhibits primary pulmonary hypertension.

62. The transgenic non-human animal of claim 60, wherein the nucleic acid is operatively linked to a promotor.

25 63. The transgenic non-human animal of claim 60, wherein the non-human animal is a mouse, a rat, a sheep, a dog, a primate or a reptile.